TERATOGENIC MEDICATION – ARE WOMEN ADEQUATELY INFORMED ABOUT THE RISKS IN PREGNANCY?

by

MAUREEN CONRADIE

Student nr: 2013183823

Mini-dissertation submitted in partial fulfilment of the requirements for the degree

Magister in Medicine in Medical Genetics

MMed (MedGen)

in the

DIVISION OF CLINICAL GENETICS

FACULTY OF HEALTH SCIENCES

UNIVERSITY OF THE FREE STATE

BLOEMFONTEIN

29 September 2017

PROMOTER: Dr BD Henderson
Head: Division Clinical Genetics
Department of Neurology
Faculty of Health Sciences, University of the Free State

CO-PROMOTOR: Dr C van Wyk
Senior Lecturer
Division Health Sciences Education
Faculty of Health Sciences, University of the Free State

DECLARATION

I hereby declare that the work submitted here is the result of my own independent investigation. Where help was sought, it was acknowledged. I further declare that this work is submitted for the first time at this university/faculty towards a Magister degree in Medicine in Medical Genetics and that it has never been submitted to any other university/faculty for the purpose of obtaining a degree.

29 September 2017

Maureen Conradie **Date**

ACKNOWLEDGEMENTS

I would like to express my gratitude to the following people who assisted me with the completion of this research project:

- My study leaders, Drs. BD Henderson and C van Wyk for their continued guidance and support through all the phases of this project.

- Ms. R Nel, Department of Biostatistics, Faculty of Health Sciences, University of the Free State (UFS), for valuable recommendations regarding the methodology of the study and assistance with the statistical analysis of the data.

- Sr. ME Motloheloa for assistance with collection of data.

- Sr. ME Gono for her assistance at the anticoagulation clinic at Universitas hospital where data was collected.

- Mrs. A Vorster, Clinical Psychologist, Support Staff for School of Medicine, Faculty of Health Sciences, UFS, for her input and advice in writing the protocol and final report.

- Dr. J Bezuidenhout, Division of Health Sciences Education, Faculty of Health Sciences, UFS, for input and advice regarding the writing of the article.

- The study participants who participated in this study.

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OVERVIEW OF RESEARCH REPORT

This research report for evaluation is structured in the format of a publishable paper. The publishable paper submitted is titled: 'Preventable warfarin-induced birth defects: A missed opportunity?' This paper will be submitted to the South African Medical Journal (SAMJ) for consideration for publication after the work has been evaluated as part of the MMed research report. SAMJ author guidelines were followed and the article is presented here in the format required. The only deviation is that the paper is presented as a single document with tables and figures included. SAMJ author guidelines are attached as appendix E.

The researcher has included an introductory chapter in order to give a more comprehensive overview of the research conducted. The protocol is not included for examination purposes since it had already been evaluated and approved within the Faculty of Health Sciences, University of the Free State, before the study commenced.

Ethics approval, information- and consent documentation, patient information pamphlets, as well the questionnaire used in the study, are included in the appendices. Only English versions of the information- and consent documentation, as well as the patient information pamphlets are included in the research report. Sesotho and Afrikaans versions of all these documents were also used during the study.

As you will notice in the protocol and questionnaire, not all data were included in the paper. Data collected in the "attitudes" section on the participants' opinions regarding pregnancy choices and termination of pregnancy will be used to compile a second paper analysing these graded and open-ended questions further. Comparisons will be made with international studies. An attempt will be made to contextualise the data in order to understand the attitudes of our local population with regards to this very sensitive topic.

CHAPTER 1: ORIENTATION TO THE STUDY

1.1 Introduction:

"Congenital anomalies are also known as birth defects, congenital disorders or congenital malformations. Congenital anomalies can be defined as structural or functional anomalies (e.g. metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth or later in life." World Health Organization (WHO) (1).

According to Mosby's Medical Dictionary a teratogen is: "any substance, agent, or process that interferes with normal prenatal development, causing the formation of one or more developmental abnormalities in the fetus. Teratogens act directly on the developing organism or indirectly, affecting such supplemental structures as the placenta or some maternal system. The type and extent of the defect are determined by the specific kind of teratogen, its mode of action, the embryonic process affected, genetic predisposition, and the stage of development at the time the exposure occurred. The period of highest vulnerability in the developing embryo is from about the third through the twelfth week of gestation, when differentiation of the major organs and systems occurs. Susceptibility to teratogenic influence decreases rapidly in the later periods of development, which are characterized by growth and elaboration. Among the known teratogens are chemical agents, including such drugs as thalidomide, alkylating agents, and alcohol; infectious agents, especially the rubella virus and cytomegalovirus; ionizing radiation, particularly x-rays; and environmental factors, such as the age and general health of the mother or any intrauterine trauma that may affect the fetus, especially during the later stages of pregnancy." (2)

According to a recent publication in the South African Medical Journal (SAMJ), at least 6.8% of births in South Africa (or one out of fifteen children born) are affected by congenital disorders or birth defects. According to the authors, 19.5% of these congenital disorders are caused by teratogens. (3) The same authors also state that Fetal Alcohol Syndrome make up a high percentage of cases in the teratogen group. Medication taken in pregnancy, however, also significantly contributes to these numbers. The number of estimated births in South Africa (SA) for 2014 according to Statistics SA is 1,207,711. (4) Applying the above percentages to the statistics of South Africa for 2014, indicates that around 82,124 children would have been born with congenital disorders in 2014 and around 16,014 of these are

potentially due to teratogens taken by a mother during pregnancy.

The United States Food and Drug Administration (FDA) has a risk category classification system to indicate the level of safety of medication taken in pregnancy. Medication is rated from A to D according to the level of safety in pregnancy and the level of supporting evidence for this. For example medication in category A is completely safe in pregnancy, while category D has proven to pose risks in humans and should be avoided, unless the benefit for the mother is greater than the expected risk. Medication in category X is contraindicated in pregnant women or women who may become pregnant, because it is known to cause birth defects in animals and humans. See Table 1 with a detailed description of the FDA pharmaceutical risk categories. (5)

Table 1: FDA pharmaceutical risk categories

Category A	Controlled trials in man have not shown fetal risk during the first trimester (and there is no evidence of risk during the second part of pregnancy); the possibility of damage to the fetus appears remote.
Category B	Reproductive studies in animals have not demonstrated risk to the fetus; controlled trials in man do not exist. Or, studies in animals show a damaging effect (other than decrease in fertility) that has not been confirmed by controlled studies in women during the first trimester (and there is no evidence of damage during the advanced stages of pregnancy).
Category C	Studies in animals have shown damaging effects on the fetus (teratogenic, lethal or other) and no controlled trials have been performed in women, or no studies are available either in man or in animals. The drug should be prescribed only if the potential benefit justifies possible risk to the fetus.
Category D	There is evidence of fetal risk in man, but benefits of use during pregnancy could be acceptable despite the risk (e.g. if the drug is necessary for survival of the patient or for severe illness when safer drugs cannot be used or are not efficacious).
Category X	Studies in animals and man have shown fetal anomalies or there is evidence of fetal risk based on human experience, or both, and the risk of using the drug during pregnancy clearly exceeds any possible benefit. The drug is contra-indicated in pregnant women or women who may become pregnant.

Several commonly prescribed medications are rated as category D or X. (5)(6)(7) Women in their reproductive ages may require these medications which could potentially cause birth defects, for the treatment of various short or long-term illnesses. See Table 2 below for a list of commonly prescribed teratogenic medication, the FDA category, along with the

indication and description of the birth defects that they can cause.

Table 2: Commonly prescribed teratogenic medication

Drug	Indication/Use	Effects in pregnancy	FDA category	Highest Risk
Thalidomide [2]	Anti-nausea drug	Limb reduction defects, abnormalities of the ear, cardiovascular system, and gut musculature. [2]	X	27th day to the 40th day of gestation
Angiotensin Converting Enzyme Inhibitors [2] Eg. Enalapril, Captopril	Anti-hypertensive	Neonatal hypotension, oliguria with renal failure, and hyperkalemia. oligohydramnios and complications thereof, prematurity, intrauterine growth retardation, and fetal death with use late in pregnancy. [2]	C (1st trimester) D (2nd and 3rd trimesters	Late in pregnancy
Coumarin derivatives [2] eg. Warfarin	Anti-clotting agent	Fetal Warfarin syndrome: nasal hypoplasia and calcific stippling of the epiphyses. Intrauterine growth retardation and developmental delay due to central nervous system damage, eye defects, and hearing loss have also been described. [2] High rate of miscarriage.	X	3 – 9 weeks gestation
Diethylstilbestrol [2]	Nonsteroidal estrogen analogue	Clear cell adenocarcinoma of the vagina, benign adenosis of the vagina, genital lesions in males [2]	X	Higher risks earlier in pregnancy
Oral contraceptives		Hypospadia in male infants	X	
Folic acid antagonists [2] eg. Methotrexate or Aminopterin	Anti-inflammatory drug. Abortification agent.	Fetal aminopterin syndrome: central nervous system defects (hydrocephalus, meningomyelocele), facial anomalies (cleft palate, high arched palate, micrognathia, ocular hypertelorism, external ear anomalies), abnormal cranial ossification, abnormalities in first branchial arch derivatives, intrauterine growth retardation and mental retardation. [2]	D, X	6 – 8 weeks gestation
Carbamazepine [2] (Tegretol®)	Anti-epileptic	1% risk for Neural Tube defects	D	1st trimester
Valproic Acid Eg. Epilim®	Anti-epileptic	Valproate syndrome: distinct craniofacial appearance, limb abnormalities, heart defects, a cluster of minor and major anomalies, and CNS dysfunction. [3]	D	1st trimester
Hydantoins [2] eg. Phenytoin®	Anti-epileptic	Fetal hydantoin syndrome: craniofacial dysmorphology (wide anterior fontanelle, ocular hypertelorism, metopic ridge, broad depressed nasal bridge, short anteverted nose, bowed upper lip, cleft lip, cleft palate), as well as variable degrees of hypoplasia of the distal phalanges, nail hypoplasia and low arch dermal ridge. Growth retardation, mental deficiency and cardiac defects are additional features of the syndrome. [2]	D	1st trimester
Isotretinoin/ Retinoids Eg. Roaccutane®	Anti-acne treatment	Retinoic acid embryopathy: craniofacial anomalies (microtia or anotia, accessory parietal sutures, narrow sloping forehead, micrognathia, flat nasal bridge, cleft	X	1st trimester

		lip and palate, and ocular hypertelorism), cardiac defects (primarily conotruncal malformations), abnormalities in thymic development, and alterations in central nervous system development. High risk for miscarriage (40%). [2]		
Misoprostol	Duodenal and gastric ulceration. Abortification agent.	Limb defects with or without Moebius' sequence. [2]	X	1st trimester
Tetracyclines	Antibiotic	Yellow-brown discolouration of teeth [2]	D	> 17 weeks gestation
Androgens [3] Eg. Danazol®	Treatment of endometriosis	Androgenic effects on female fetus [3]	X	
Lithium	Mood-stabilizer	Associated with fetal and neonatal cardiac arrhythmias, hypoglycemia, nephrogenic diabetes insipidus, polyhydramnios, changes in thyroid function, premature delivery, LGA infant, and "floppy infant" syndrome. Congenital cardiac defects – Ebstein anomaly [3]	D	1st trimester
Benzodiazepines Eg. Valium®	Anxiolytics	Some studies show increased risk of oral clefts with first trimester exposure. Prolonged CNS depression can occur, with symptoms including mild sedation, hypotonia, reluctance to suck, apneic spells, cyanosis, impaired metabolic responses to stress, "floppy infant" syndrome, and marked neonatal withdrawal that can persist for hours to months after birth. [3]	D	Whole pregnancy
Antithyroids	Antithyroids for treatment of Graves'disease	Fetal hypothyroidism [3]	D	
Radioactive iodine	Treatment for hyper-thyroidism	Destruction of fetal thyroid	X	

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2. Dutta S. Review Article Human Teratogens And Their Effects : A Critical Evaluation. *Int J Inf Res Rev*. 2015;2(March):525-536.
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Warfarin is one of a group of medications called Coumadin derivatives, anticoagulants used in patients with an increased risk for thromboembolic events. Indications for warfarin use would be prosthetic heart-valve replacements, inherited or acquired thrombophilias (conditions that predispose to spontaneous and inappropriate venous clotting), cardiac arrhythmias and the prevention of recurrent pulmonary embolism. Coumadin derivatives

acts by inhibiting vitamin K-dependant clotting factors which include factors II, VII, IX, and X, and the anticoagulant proteins C and S. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K-dependent clotting factors. (8)

In South Africa we have a high burden of pre-existing cardiac abnormalities among young women. Rheumatic heart disease is still very prevalent in sub-Saharan Africa. (9) Therefore there are a large number of young women who have had heart valve replacements and need to be on life-long warfarin treatment.

In pregnancy, warfarin crosses the placenta and results in an embryopathy, "Fetal Warfarin Syndrome" (most likely through its inhibition of vitamin K), especially in the 6^{th} to 9^{th} week of pregnancy. It also results in effects in the 2^{nd} and 3^{rd} trimester, involving the central nervous system, most likely due to microhaemorrhages. The "Fetal Warfarin Syndrome" consists of nasal hypoplasia, microphthalmia, hypoplasia of the extremities, intra-uterine growth retardation, cardiac lesions, scoliosis, deafness, and intellectual impairment. (7)(10)

The incidence of birth defects due to teratogenic medication is higher in middle- and low-income countries according to the March of Dimes Global Report on Birth defects of 2006. The authors postulate that this is due to the regulation of some of these medications not being as strict as in high-income countries, which result in it being readily available over the counter. Multiple drug use is common, the awareness of the teratogenic potential of certain medications is lacking and most women are unaware of their pregnancy during the first few weeks. (11)

In the case of warfarin (Coumadin derivatives), it appears from studies done locally that the incidence of birth defects in pregnancy is higher than the international figures. According to an international reference source, about 70% of pregnancies exposed to Coumadin derivatives (including warfarin) are expected to result in a normal infant (therefore 30% of pregnancies end in a miscarriage, stillbirth or with fetal abnormalities). (10) Exposure between the 6^{th} and 9^{th} weeks of gestation is associated with "Fetal Warfarin syndrome" with an incidence of up to 25% or greater. (10) These figures are similar to other published information. (7) Gregerson found in 2005 that 52% of women with heart valve replacements on warfarin anticoagulation in Johannesburg had poor obstetric or fetal outcomes. (12) Another study done in Kwazulu-Natal found that out of 61 women, 41 (67%) had live births.

The other women had miscarriages, stillbirths or early neonatal deaths. (9)

Birth defects due to teratogenic medication in pregnancy are potentially avoidable if both patients and health care providers are adequately informed about the risks in pregnancy. Patients should also be informed about adequate contraceptive measures and plan their pregnancies. Pre-conception care is very important for women using chronic medications. (13) Before an intended pregnancy, treatment regimes can be optimized by either changing medication to the safest alternatives, prescribing the lowest possible doses or adding supplements that are known to counteract certain teratogenic effects of medications, e.g. Folic Acid supplementation for women on anti-convulsant treatment. (14) Access, availability and appropriate referral to Genetic Counselling services and Feto-Maternal clinics would also help to ensure that these patients are managed correctly before and during the pregnancy.

Babies born with birth defects due to teratogenic medications are regularly seen at genetics clinics and by paediatricians locally. Accurate statistics of the incidence of congenital malformations in pregnancies exposed to teratogenic substances are not available in South Africa. From the experience of the authors, the mothers usually had no knowledge of the teratogenic potential of the medication they were using and had not taken the necessary contraceptive precautions.

Gregerson found in her 2005 study among women in Johannesburg using warfarin that the study participants lack knowledge about the effects of warfarin in general, the effects of warfarin in pregnancy, the need for planned pregnancies and what management options are available to them. (12)

From clinical experience, the authors hypothesise that our population of patients in the Free State, and most likely in other parts of the country, do not have adequate knowledge about the teratogenic potential of the chronic medication that they are using or appropriate knowledge about effective contraceptive methods to avoid an undesired pregnancy.

There have been multiple studies done internationally evaluating patients' knowledge and practice with regards to their warfarin treatment in terms of side-effects of bleeding, precautions, monitoring of levels and emergency management. A few standardised

questionnaires were verified to test patients' knowledge about these aspects. (15) No questions were included about the negative effects of use in pregnancy in terms of birth defects. Therefore further research is needed in terms of patient knowledge, attitudes and practice with regards to the effects of teratogenic medication in pregnancy.

The purpose of doing this study was to determine the knowledge, attitudes and practice of women using warfarin, a known teratogenic medication, regarding the risks for birth defects. The intention was that if patients experienced a lack of knowledge or desired more information this could be used as motivation and planning for an intervention strategy.

It is the responsibility of all health care providers to ensure that patients are adequately informed of the risks of birth defects associated with the chronic medication they are started on; that they are equipped to make informed pregnancy choices by using efficient methods of contraception; and to strive to reduce the incidence of birth defects due to teratogenic medication.

This study only focused in detail on women using warfarin at a clinic in Universitas hospital. Further studies will be needed to evaluate the knowledge, attitudes and practice of women at primary care level and in rural areas, as well as women using other category X medications. The knowledge, attitudes and practice of health care providers (i.e. doctors, nurses and pharmacists), regarding teratogenic medications and the barriers to health care providers properly informing their patients will also need to be investigated.

The intention is to publish the findings of this study in an influential Southern African journal. The findings were also presented at an international Medical Genetics Workshop in Italy in 2016 and presented at the South African Society of Human Genetics Congress in 2017 in poster format.

1.2 Aim of the study:

The aim of this study was to determine the knowledge, attitudes and practice of women of reproductive potential on chronic warfarin therapy regarding the risk of this medication in pregnancy.

1.3 Study design:

This was a descriptive study collecting quantitative data on the knowledge, attitude and practice of women using chronic warfarin therapy.

1.4 Methodology:

A literature study was conducted on research done previously, internationally and locally, on the topic of teratogenic medication, as well as the knowledge, attitudes and practice of women on chronic teratogenic medication. This information was used to construct the questionnaire survey and develop the information documents for the patients.

A questionnaire survey was conducted among women of reproductive age on chronic warfarin therapy focussing on their knowledge, attitudes and practice with regard to the teratogenic potential of the medication they are using.

1.5 Sample:

Reproductive age in this study was defined as between age 15 to 49 years as this is the age group used by Statistics SA in previous publications about fertility in South Africa (16).

The specific population group targeted in this study was women in their reproductive ages on warfarin therapy. Patients on warfarin therapy attend anticoagulation clinics to have coagulation studies done every 2 to 8 weeks as part of their routine care. This study was conducted at the anticoagulation clinic at Universitas hospital to facilitate easy access tothe participants. According to the nursing staff at the clinic, around 300 women between the ages of 15 and 49 attend the clinic on a regular basis.

The clinic runs Mondays to Fridays, with patients arriving between 07h00 and 13h00 every day. They have their blood taken and then wait for the results to have their dose of warfarin adjusted according to the blood level. The plan was that the researcher should be able to conduct approximately 5 interviews per day and would be able to collect data for 3 days a week for 6 to 8 weeks. Consequently it was estimated that 90 to 120 patients could be interviewed as part of the study.

Convenience sampling was used, and patients interviewed after their blood samples were

taken, if they fulfilled the inclusion criteria. Inclusion criteria were women between the ages of 15 and 49 years, currently using warfarin therapy and attending the anticoagulation clinic at Universitas. Women or parents/guardians not competent to give informed consent were excluded from the study as well as women who were not able to comprehend English, Afrikaans or Sesotho.

1.6 Measurement:

Participants eligible for the questionnaire survey were informed of the study by the sister in charge of running the coagulation clinic upon arrival at the clinic. She provided information regarding the study and asked if they would like to participate. An information sheet and the consent form were given to them to read while they were waiting to have their blood taken. The researcher or assistant officer approached the interested participants individually. After the blood specimen had been taken, they were directed to a private room where the consent form was discussed in detail. The participants were asked to explain what they were told or what they had read in order to check their understanding of the consent process. After this information process, if they agreed to participate, they signed the informed consent document. The researcher or assistant officer then proceeded to administer the questionnaire [see Appendix C] to obtain the study data. The assistant officer was a nursing sister fluent in Sesotho, with counselling experience and background knowledge of congenital abnormalities. She administered the questionnaire in the case of Sesotho speaking participants who do not understand English or Afrikaans. She was appointed on a private contract basis to help with the research.

The questionnaire focused on the following aspects: 1) demographic data; 2) the duration and indication of warfarin therapy; information about gravidity, parity and children born with congenital abnormalities; relationship status, sexual activity and practice with regards to contraceptive use; 3) patient knowledge of the teratogenic potential of warfarin, contraceptive use and the procedure when a pregnancy is desired; and 4) the attitudes and opinions of women about various aspects with regards to teratogenic medication, methods of information delivery, pregnancy choices and termination of pregnancy. The questionnaire contained mostly closed-ended questions, some open ended questions, multiple choice questions and graded questions regarding opinions.

The advantage of a researcher administered questionnaire was that the data sets were more complete, questions could be clarified, and there was greater control of the environment. The disadvantage was that it took up more of the researcher's time, only a limited number of participants could be interviewed and there could be some degree of interviewer bias.

The collection of data in the form of the researcher administered questionnaire was over an 8 week period as this overlaps with the interval at which the patients usually visit the clinic. A list of participants was kept with the consent forms to ensure that they were only included in the study once. The interval of data collection was kept as short as possible to minimise the participants informing each other and thereby influencing the results of the study.

After the questionnaire had been completed, an information leaflet in English, Afrikaans or Sesotho was given to each participant. This information leaflet was designed for our setting and aimed at primary school literacy level in order to be clearly understandable. These information leaflets informed the participant of the teratogenic effects of warfarin and also gave advice on appropriate contraceptive measures and the advantage of family planning [see Appendix D]. Information leaflets were handed to participants in a sealed envelope to be opened at home, so as not to influence the other participants attending the clinic on the same day.

After completion of the questionnaire, the data were entered into an Excel spreadsheet by the researcher. Data verification was done by entering all data twice in 2 separate data sheets. The data were then handed to the Biostatistics department for analysis.

1.7 Methodological and measurement errors:

We attempted to minimize incomplete data sets by doing researcher administered questionnaires. We ensured that the questions were understood and answered correctly, thus the quality of data is of a high level. We were also able to include illiterate patients in the study which would not have been possible by participant-completed questionnaires.

This method unfortunately limited sample size due to time constraints as only one or two participants were able to participate at any given time. This took up more time dedicated to research.

Language barriers were addressed by having a Sesotho speaking nursing sister assisting with the questionnaires. Participants unable to understand English, Afrikaans or Sesotho were excluded from the study. This may have resulted in a bias against patients of other languages. According to the Stats SA census of 2001, however, the primary home language distribution of the Free State is as follows: 64.4% Sesotho, 11.9% Afrikaans and 1.2% English. These 3 languages therefore covered ± 78% of the population of the Free State in terms of home language and more in terms of a spoken or understood language.

The identification of participants relied on the nursing staff at the anticoagulation clinic and this could have potentially limited the study participation due to a lack of motivation on the side of the nursing staff or patient loads at the clinic. We did not experience this in practice.

The study was conducted at the anticoagulation clinic at Universitas hospital only. This resulted in a theoretical bias towards participants of certain demographics as this is a tertiary unit in an urban area. Patients on warfarin from other areas in the province have their anticoagulation levels checked at their primary or secondary care facilities. We took into consideration that our study was potentially not representative of the true population in the province.

1.8 Pilot study:

A pilot study was undertaken to determine if the questionnaire is easily understandable. This included the first 5 patients from the anticoagulation clinic. The plan was that if no major changes to the questionnaire were required, these subjects would be included in the main study.

1.9 Data analysis:

Descriptive statistics, namely means and standard deviations or medians and percentiles for continuous data and frequencies and percentages of categorical data, were calculated. The analysis was done by the department Biostatistics, UFS.

1.10 Budget:

Expenses included paper and cartridges for printing the consent forms, data sheets and

information leaflets; envelopes for the information sheets; and translation costs of translating the informed consent forms and information leaflets to Sesotho. An assistant officer was employed to assist with the data collection.

These costs were covered out of research funds from the Department of Neurology and funding from the School of Medicine, UFS.

Pregnancy tests were obtained from the Gynaecology clinic as the study participants are all registered patients at Universitas hospital and performing pregnancy tests would contribute to their care. This was only necessary in one case.

1.11 Ethical considerations:

Permission to perform the research was obtained from the Free State Department of Health after approval from the Ethics Committees of the UFS and FSDoH. The CEO of Universitas hospital was informed in writing of the study after the above permissions were granted. Permission was granted in writing from the Laboratory manager of the National Health Laboratory Services (NHLS) and the head of the department of Haematology at the NHLS to proceed with the research after approval by the Ethics Committee and the FSDoH. The anticoagulation clinic falls under their jurisdiction.

Informed consent was obtained from the participants before the structured interview in the form of a brief discussion and a more detailed consent form that was available in English, Afrikaans and Sesotho [see appendix B for the English version]. For illiterate patients, the consent form was read in their preferred language (English, Afrikaans or Sesotho). A nursing sister competent in Sesotho assisted where participants were Sesotho speaking only. Participation was entirely voluntary and any participant could withdraw from the interview at any time. It was also made clear that refusal to participate in the study or withdrawal would not impact on the quality or other aspects of their care. Participants that were incompetent to give informed consent due to intellectual disability were excluded from the study.

In the case of minors (15-17 years), assent from the individual would have been sought and if the caregiver or guardian was present and the minor assents to their involvement, they would have been asked for consent. The Choice on Termination of Pregnancy Act of 1996

makes provision for women of any age (minors included) to decide on termination of pregnancy. Minors are allowed to continue by their own choice with termination of pregnancy without consent from their parents or legal guardians, but should be advised to discuss the matter with them (17). Our study focused on essential knowledge with regards to the teratogenic potential of medications that these minors are taking on a chronic basis. As there is a risk of birth defects if these minors do fall pregnant, we considered the information that would have been given as part of study participation, essential for them to make informed choices. Taking into consideration the view of the Choice on Termination of Pregnancy Act of minors being able to consent to terminations independently, this should also have made allowance for them to participate in this study by own choice as this involves potential pregnancy and possible grounds for termination of pregnancy. There were no minors included in the study as they were not present among the participants during the time period the sampling took place.

During the structured interviews, data sheets were numbered and no identifying information was needed. For demographic purposes the age (not the date of birth) as well as the residential suburb (rather than the address) was recorded in order to protect participant confidentiality. The consent forms are safely store in a secure cabinet in a private locked office. Privacy during the interview was upheld by conducting the interviews in a private room or office.

When a participant was found to be pregnant, she was referred to the High Risk Antenatal clinic at Universitas for a detailed evaluation and further management. If there was a suspicion of a possible pregnancy, a urine pregnancy test was offered to the patient and if positive she was referred as stated above. As with the above issue of consent, the same principles would have applied to minors if found to be pregnant or possibly pregnant, according to the Choice on Termination of Pregnancy Act 1996 (17). They would have been advised to discuss the issue with a parent or legal guardian, but could not be forced to do so.

The advantage of study participation for the individual was obtaining essential and correct information about the risks associated with the use of teratogenic medication in pregnancy, the efficient use of contraception and the advised route to follow if a pregnancy is desired. This would hopefully lead to informed family planning choices in this high risk group of women, thereby lowering the woman’s risk for delivering a baby with a congenital disorder.

The information leaflets were made available to the anticoagulation clinic for all women attending the clinic in future. The benefit for the general population is that this intervention could contribute to lowering the number of babies born with congenital malformations due to preventable causes.

Through conducting the study, awareness was created among health care providers on a small scale at Universitas hospital. Through publication of the findings, the hope is that awareness would be created on a national scale among health care providers and policy makers.

Participants did not receive any monetary remuneration for study participation. There were no additional costs for them to be involved in the study as they participated at a time when they attended a scheduled clinic as part of their routine warfarin therapy follow up.

The potential negative effects of study participation included anxiety for the participants due to information regarding the teratogenic potential of their medication. The nature of information could have potentially led to a participant being faced by a difficult decision if found to be pregnant and if congenital malformation are subsequently diagnosed. The plan was that if there was deemed to be significant emotional distress and clinical risk, these participants would have been referred for appropriate psychological evaluation and therapy. None of the women in the study experienced significant emotional distress as a result of study participation. Women that do want to fall pregnant received information on how to proceed with this in the information sheet.

1.12 Implementation:

The value of the study was to identify a potential area of intervention that would address the information given to women initiated on any teratogenic medication with regards to the effects of the medication in pregnancy, contraceptive guidelines and the route to follow if a pregnancy is desired.

This study forms a baseline from which to compare future interventions. On a larger scale, this study could also contribute to lowering the incidence of preventable congenital malformations due to teratogenic causes.

CHAPTER 2: PUBLISHABLE ARTICLE

Title:

PREVENTABLE WARFARIN-INDUCED BIRTH DEFECTS: A MISSED OPPORTUNITY?

Format:
As for submission to SAMJ [see Appendix E]

Preventable warfarin-induced birth defects: A missed opportunity?

M Conradie[1], BD Henderson[2], C van Wyk[3]

1. *MBChB, DCH, FCMG (SA). Registrar, Division Clinical Genetics, University of the Free State (UFS), Bloemfontein, South Africa (SA). Email:conradiemaureen@gmail.com*
2. *MBChB, DCH, MMed (Paed). Head Clinic Unit, Division Clinical Genetics, UFS, Bloemfontein,SA. Email: gnmgbdh@ufs.ac.za*
3. *MSc (Med) Genetic Counselling, PhD (Health Professions Education). Senior Lecturer, Division of Health Sciences Education, Faculty of Health Sciences, UFS, Bloemfontein, SA. Email: vanwykc2@ufs.ac.za*

Abstract

Background: Congenital abnormalities and pregnancy losses due to the teratogenic effects of warfarin are still prevalent among the South African population. This is potentially preventable if the challenges and barriers faced by at-risk women are understood and addressed effectively.
Objectives: To determine the practice, knowledge and attitudes regarding the teratogenic risks experienced by women on warfarin.
Methods: A descriptive study was performed. Quantitative data were collected through a researcher-administered questionnaire. The target population comprised of 101 women of reproductive age who took warfarin treatment and attended a single tertiary level anticoagulation clinic.
Results: Language barriers, poor understanding of basic terminology and mathematics, poor contraceptive and family planning practices, lack of knowledge regarding the risks of warfarin in pregnancy and passive attitudes towards information attainment are patient related challenges identified in this study.
Conclusion: Interventions are necessary to address the challenges in such settings. This includes increased awareness of the teratogenic potential of specific chronic medications among health care providers, patients and the public. Standardised management protocols of women of reproductive age initiated on teratogenic medications should be implemented. Better education of patients is needed regarding contraceptive methods and family planning. Improvement of the counselling skills of health care providers and the availability of translators or health care providers fluent in local languages could assist in risk reduction.

Introduction

'Congenital disorders or birth defects are defined as structural or functional anomalies that occur during intrauterine life and can be identified prenatally, at birth or later in life'.[1]

A teratogen is any substance, agent, or process that interferes with typical fetal development, resulting in one or more congenital disorder in the fetus. The type and severity of the defect are determined by the kind of teratogen, its mode of action, the embryonic process affected, genetic predisposition, and the stage of development at the time of the exposure. The period of highest vulnerability in the developing embryo is from about the third through to the twelfth week of gestation. This is when differentiation of the major organs and systems

occurs. Among the known teratogens are chemical agents, including drugs such as thalidomide, alkylating agents, and alcohol; infectious agents, especially rubella-, cytomegalo- and more recently zika virus; ionizing radiation; and environmental factors, such as the age and general health of the mother or intrauterine trauma.[2]

The incidence of birth defects due to teratogenic medication is higher in middle- and low-income countries according to the March of Dimes Global Report on Birth defects of 2006. The authors postulate that this is due to the regulation of some of these medications being less strict, resulting in over the counter availability. Multiple drug use is common, the awareness of the teratogenic potential of certain medications is lacking and most women are unaware of their pregnancy during the first few weeks.[3]

A recent publication in the South African Medical Journal (SAMJ) stated according to modelled data that at least 6.8% of births in South Africa (or one out of fifteen children born) are affected by congenital disorders or birth defects. According to the authors, 19.5% of these congenital disorders are caused by teratogens. Fetal Alcohol Syndrome make up a high percentage of cases in the teratogen group,[4] however medication taken in pregnancy, also contributes to these numbers significantly.

Warfarin, a vitamin K inhibitor, is an anticoagulant used in patients with an increased risk for thromboembolic events. Indications would be prosthetic heart-valve replacements, inherited or acquired thrombophilias, cardiac arrhythmias and the prevention of recurrent pulmonary embolism.[5] In South Africa we have a high burden of pre-existing cardiac abnormalities among young patients due to a high prevalence of rheumatic heart disease, resulting in a large number of young women with prosthetic cardiac valves that necessitates life-long anticoagulation.[6,7]

In pregnancy, warfarin crosses the placenta and results in an embryopathy, with an especially high risk of abnormalities in the 6th to 9th week of gestation (25% or greater risk). It may also result in central nervous system abnormalities in the 2nd and 3rd trimester, likely due to microhaemorrhages. The ‘Fetal Warfarin Syndrome’ consists of nasal hypoplasia, microphthalmia, hypoplasia of the extremities, intra-uterine growth retardation, cardiac anomalies, scoliosis, deafness and mental retardation.[8,9] Additionally the risk for miscarriages or stillbirths in pregnancies exposed to warfarin increases significantly.

Limited studies have investigated the perspectives and practices of women exposed to potentially teratogenic substances in order to identify high risk behaviour and attitudes that could contribute to congenital abnormalities due to teratogenesis.[10-12]

Studies have been done internationally evaluating patients’ knowledge and practice with regards to their warfarin treatment in terms of side-effects of bleeding, precautions, monitoring of levels and emergency management. A few standardised questionnaires were verified to test patients’ knowledge about these aspects.[13,14] No questions were included about the negative effects of use in pregnancy in terms of birth defects. A local study among women in Johannesburg using warfarin found that they lack knowledge about the effects of warfarin in general, the effects of warfarin in pregnancy, the need for planned pregnancies and what management options are available to them.[15]

In order to lower the incidence of congenital disorders due to teratogenesis there needs to be a focus on understanding the challenges and barriers that play a role in this process and

addressing these effectively. This study evaluated the practice, knowledge and attitudes of women of reproductive potential taking warfarin, regarding the risk of this medication in pregnancy.

Objectives

Poor pregnancy outcomes in the form of congenital abnormalities or pregnancy losses due to the effects of warfarin in pregnancy are still regularly seen in South Africa. Epidemiological data and statistics on the exact incidence are not available.

The main objective of this study was to determine the practice, knowledge and attitudes of women of reproductive potential taking warfarin, regarding the risk of this medication in pregnancy. The findings may serve to highlight the specific challenges in South African settings and aims to provide recommendations.

Methods

A descriptive study was done, collecting quantitative data through a researcher-administered questionnaire. Women of reproductive age, defined as between the ages of 15 and 49 years currently on warfarin treatment were included in the study. Participants not able to give consent or converse in Sesotho, English or Afrikaans were excluded. Convenience sampling was used by approaching attendants of a specialist anti-clotting clinic in a tertiary hospital.

The study was explained by the researchers, a written information sheet about the study provided, written consent obtained and the data collected. Data collection was over a period of 8 weeks.

The questionnaire focused on the following aspects: 1) demographic data; 2) details about the initiation of warfarin; information about gravidity, parity and pregnancy outcomes; relationship status, sexual activity and practice with regards to contraceptive use; 3) patient knowledge of contraceptives and the teratogenic potential of warfarin; and 4) the attitudes and opinions of women about various aspects with regards to the teratogenic medication and methods of information delivery.

Information pamphlets were given to participants in a sealed envelope after completion of the questionnaire. This served as education on the teratogenic effects of warfarin and gave advice on appropriate contraceptive measures and family planning.

Statistical analysis was done by the local Department of Biostatistics. Descriptive statistics, namely means and standard deviations or medians and percentiles for continuous data and frequencies and percentages for categorical data, were calculated.

Ethical approval for the study was obtained from the Health Sciences Research Ethics Committee of the University of the Free State (HSREC nr 205/2015) and the Department of Health, Free State.

Results

Demographics

A total of a 101 women participated in the study. The median age of participants was 34 years with a range from 18 to 49 years. The participants resided in urban, as well as rural areas.

The highest education level was stated in *n* = 98/101:. *n* =10 (10.2%) had an education level of grade 7 or below, *n* = 12 (12.2%) grade 8 or 9, *n* = 65 (63.3%) grade 10 to 12 and *n* = 11 (11.2%) reported a tertiary education. A total of *n* = 50/101 women (49.5%) indicated they are currently single, separated or widowed and the remaining *n* = 51/101 (50.5%) reported being in a casual or full-time relationship. A large number of participants *n* = 76/101 (75.3%) indicated that they were unemployed at the time of the study, with *n* = 33/101 (32.7%) living off government subsidies only.

The home language reported by participants in decreasing order of speakers was Sesotho *n* = 63/101 (62.4%), Afrikaans *n* = 16/101 (15.8%), Tswana *n* = 13/101 (12.9%), isiXhosa or Zulu *n* = 7/101 (6.9%) and English *n* = 2/101 (2%).

Practice

The most common indications for warfarin use were heart valve replacements *n* = 44/101 (43.6%) and deep venous thrombosis *n* = 43/101 (42.6%). The duration of treatment ranged from 1 week to 32 years, with a median duration of 4 years. Departments that initiated warfarin in the largest number of people in our study population were adult cardiology at a tertiary level *n* = 37/101 (36.6%) and general medicine departments at primary care level *n* = 25/101 (24.8%).

We asked the participants to indicate whether they had a pregnancy test prior to the initiation of warfarin: *n* = 32/101 (31.7%) indicated that they were tested; *n* = 36/101 (35.6%) that no pregnancy test was done; *n* = 19/101 (18.8%) were unsure and in *n* = 14/101 (13.9%) doing a pregnancy test would not have been applicable (8 women were already pregnant; 5 were under the age of 15 years and 1 had undergone tubal ligation). Almost two thirds of women *n* = 62/101 (61.3%) admitted to taking additional chronic medication of which the most common were unspecified ‘cardiac’ drugs, antiretrovirals and antihypertensives.

With regards to sexual activity *n* = 25/101 (24.8%) said they were not currently sexually active, the remainder *n* = 76/101 (75.2%) admitted to being in a sexual relationship. Out of these participants *n* = 15/76 (19.8%), were not using any contraception and another *n* = 15/76 (19.8%) were only using male condoms.

When asked about single vs double contraception, out of the 70 women that did use contraception, *n* = 16/70 (22.9%) were using 2 different methods of contraception. Among the women who do use contraception, *n* = 8/70 (11.4%) admitted to not using it regularly. Seventeen out of a hundred *n* = 17/100 (17%) women reported ever having asked for contraceptive advice and this was mostly from the nursing sister at the local clinic.
Among the 101 women, 87 had been pregnant at least once. A total of 209 pregnancies were reported in this group of which 110 were planned *n* = 110/209 (53%). Twenty six out of the

87 women *n* = 26/87 (30%) had used warfarin during one or more of their pregnancies. Pregnancy outcomes of 208 out of the 209 pregnancies as reported by the mothers are indicated in Fig. 1. One live birth was excluded from these calculations as this is a child diagnosed by our department with fetal warfarin syndrome. In all of the other cases pregnancy outcomes were reported by the participants and cases of fetal warfarin syndrome in this group cannot be excluded as it is not known if the children were specifically evaluated by a geneticist or paediatrician for related birth defects.

A third of the participants *n* = 32/100 (32%) indicated that they are planning future pregnancies.

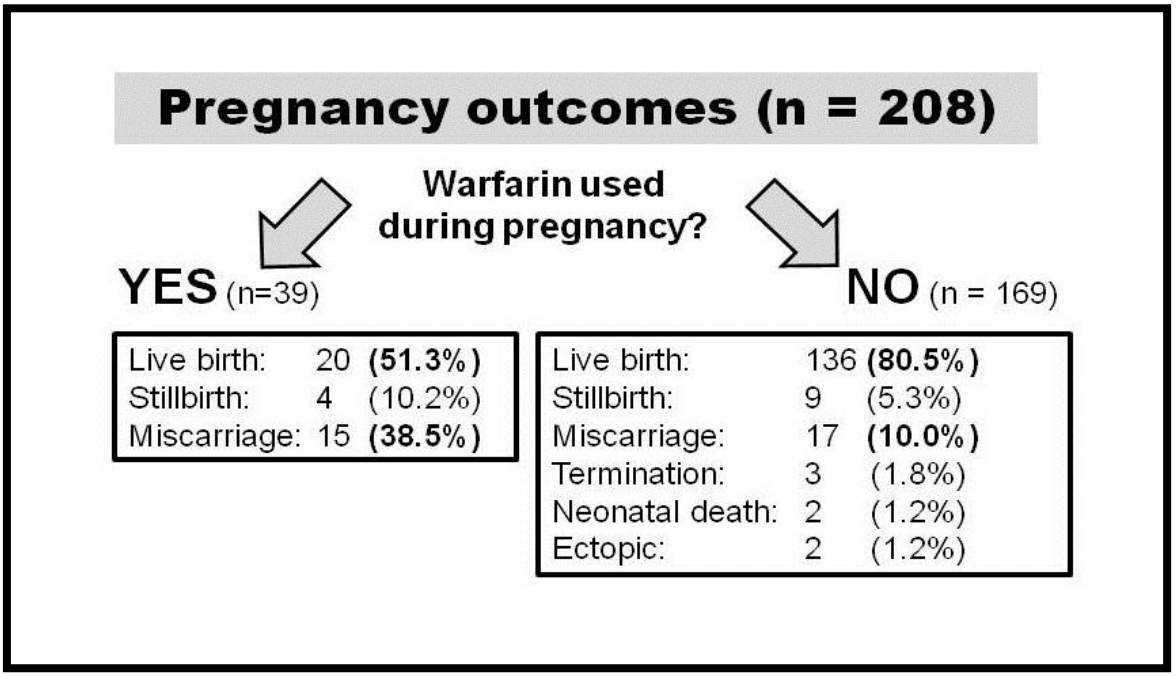

Figure 1. Pregnancy outcomes in warfarin exposed versus unexposed pregnancies.

Knowledge

Less than half of the women *n* = 47/101 (46.5%) indicated that they were informed about the effects of warfarin in pregnancy. Of these, *n* = 24/47 (52.2%) received this advice from their doctor and *n* = 18/47 (39.1%) from the nursing sister at the clinic.

The majority of the participants *n* = 89/100 (89%), had no concept or understanding of the term 'birth defects'. An open ended question about substances that participants consider to be harmful to a fetus during pregnancy, elicited truly teratogenic substances (e.g. alcohol was listed by 65 participants), but also inappropriate substances or exposures (e.g. lack of exercise).

Participants' concept of risk was evaluated. Three different ways of stating the same risk was presented and participants asked to indicate the 'highest risk' out of these: 1) 10% percent, 2) one out of ten, 3) ten out of a hundred. Additionally they could indicate that all the statements are the same. Out of these *n* = 39/101 (38.6%) selected option 1; *n* = 10/101

(9.9%) selected option 2; *n* = 22/101 (21.8%) option 3; and *n* = 30/101 (29.7%) indicated correctly that all these expressions of risk are the same.

Almost half of the women *n* = 47/101 (46.5%) thought that the period of highest risk for congenital abnormalities in a pregnancy does not differ between trimesters. Thirty-nine *n* = 39/101 (38.6%) thought that the first 3 months have the highest risk, *n* = 5/101 (5%) thought the second 3 months, and the remaining *n* = 10/101 (9.9%) either thought the last 3 months (9) or were uncertain (1).

The chance of warfarin causing abnormalities in the baby when taken in pregnancy was estimated to be 5% by *n* = 30/101 (29.7%), 30% by *n* = 17/101 (16.8%), 90% by *n* = 22/101 (21.8%), 100% by *n* = 29/101 (28.7%) and unsure by *n* = 3/101 (3%). Knowledge about the specific congenital abnormalities known to be caused by warfarin was evaluated and results are given in Table 1. As indicated by this data, most women either thought that these specific abnormalities could not be caused by warfarin, or were uncertain if it could.

Table 1. Participants' knowledge about specific abnormalities caused by warfarin.

	Yes ***n/101*** **(%)**	**No** ***n/101*** **(%)**	**Unsure** ***n/101*** **(%)**
Can warfarin cause brain abnormalities?	8 (7.9)	32 (31.7)	61 (60.4)
Can warfarin cause abnormalities of the bony structure or skeleton?	9 (8.9)	43 (42.5)	49 (48.5)
Can warfarin result in abnormalities of the baby's nose with breathing problems?	8 (7.9)	42 (41.6)	51 (50.5)

Knowledge of the reliability of contraceptive methods was assessed by asking which method of contraception among the options given has the lowest chance of a pregnancy: *n* = 61/101 (60.4%) said injectables or oral contraceptives, *n* = 26/101 (25.7%) male condoms, *n* = 11/101 (10.9%) female condoms and *n* = 3/101 (3.0%) checking the calendar.

Attitudes

Fifty-two participants *n* = 52/101 (51.5%) thought they did not have enough information about warfarin in pregnancy, *n* = 38/101 (37.6%) were satisfied about having enough information and *n* = 11/101 (10.9%) were unsure about this. The ones that indicated that they did not have enough information were asked to indicate reasons for this. Out of the 51 women that answered this question, *n* = 27/51 (52.9%) said they were 'never given the information', *n* = 12/51 (23.5%) indicated that they 'did not ask for information', *n* = 4/51 (7.8%) 'did not understand the explanation', *n* = 3/51 (5.9%) 'were given information, but forgot because no written material was provided', *n* = 2/51 (3.9%) 'did not understand the language the information was given in' and the other *n* = 3/51 (5.9%) gave other reasons.

Most women *n* = 69/101 (68.3%) felt that it was the responsibility of their doctor to inform them about the effects of medication in pregnancy, while *n* = 12/101 (11.9%) thought this responsibility should fall on the nurse at the clinic, *n* = 1/101 (1%) thought it should be the pharmacist's role and *n* = 19/101 (18.8%) indicated that all of the above health care providers should be involved. Most participants *n* = 81/101 (80.2%) indicated that they would like more information about the risks of their medication in pregnancy. The preferred method of information transfer was assessed and these results are tabulated in Table 2. The overwhelming majority of participants *n* = 74/101 (73.3%) preferred a counselling session that is translated to their home language.

Table 2. Information delivery preference.

Method of information delivery	***n/101* (%)**
Posters in the clinic	6 (5.9)
Information leaflets in English	2 (1.9)
Information leaflets in home language	9 (8.9)
Counselling session in English	5 (4.9)
Counselling session translated to my home language	74 (73.3)
Pharmacist explaining prior to handing out medication	4 (3.9)
Warnings printed on the medication box	4 (3.9)

Discussion

Practice

Counselling about the potential risks in pregnancy and appropriate contraceptive measures, as well as performing a pregnancy test, should form an important part of the protocol of initiating a potentially teratogenic medication, including warfarin, in a woman of reproductive age. Guidelines are available internationally,[16,17] but it is uncertain if these protocols and guidelines are implemented in practice. This responsibility falls on the health care provider initiating the medication. Care should be taken to counsel all females that are initiated on warfarin in childhood, prior to the onset of puberty.

Among our study participants, all levels of care, including primary and tertiary services, were involved in initiation of warfarin. This emphasises the fact that health care providers involved in different levels of care should all be equipped to deal with this process or be aware of the need for counselling. Only a third *n* = 32/87 (36.8%) of the participants in whom a pregnancy test prior to initiation would have been indicated, did report it being done.

Health care providers are possibly not aware of these practice guidelines and continuation of care in the government sector is a challenge due to rotating staff members. Recall by the

participants could have been deficient. Further exploration of this result was outside the scope of the study.

The number of study participants admitting to currently being sexually active *n* = 76/101 (75.2%) was higher than the number that indicated they are in a casual or full time relationship *n* = 51/101 (50.5%). This discrepancy could be explained by short-term sexual encounters with a resulting high risk for unplanned pregnancies and sexually transmitted diseases if effective contraceptive practices are not adhered to. Contraceptive practices were poor with *n* = 30/76 (39.5%) of women admitting to be sexually active, not using any contraception, or using only male condoms. Additionally contraception was not always used regularly. Effective family planning strategies are important to prevent unplanned pregnancies and reduce the risk of babies born with congenital abnormalities.

Outcomes of pregnancies

The live birth rate in the pregnancies of the women in our study exposed to warfarin was much lower *n* = 20/39 (51.3%) versus the pregnancies not exposed to warfarin *n* = 136/169 (80.5%) in this same population. Conversely the rate of pregnancy loss was much higher in the warfarin exposed pregnancies due to stillbirths and miscarriages.

According to international figures, about 70% of pregnancies exposed to Coumadin derivatives (including warfarin) are expected to result in a normal infant (therefore 30% of pregnancies end in a miscarriage, stillbirth or with fetal abnormalities).[8,9] A local study of women in Johannesburg with heart valve replacements on warfarin had poor fetal outcomes in 55.2% of warfarin exposed pregnancies.[15] In another study done in Kwazulu-Natal the findings were closer to international figures where *n* = 41/61 (67%) had live births.[6] A multitude of factors are potentially responsible for the poorer pregnancy outcomes in our local population. This includes socio-economic factors, the high burden of infective diseases, inadequate health care services for this high risk group, unequal access to care and patient factors like late-booking and language barriers.

Knowledge

Education level was high in this population group with *n* = 76/98 (77.6%) participants having attained at least grade 10. This contrasts strongly to the poor level of understanding of basic terminology and mathematics needed to understand the concepts of teratogenesis. 'Birth defects' is a layman's term commonly used in medical practice during the counselling of patients. In the group of women interviewed *n* = 89/100 (89%) had no understanding of what this term means. Risk is usually expressed as a percentage or a number out of a hundred or thousand for instance. The majority of the study participants *n* = 71/101 (70.3%) had no understanding of these expressions of risk and how to interpret it. Risk is known to be a very difficult concept to understand and does take a fair amount of skill and counselling experience in order to convey this during a counselling session.[18]

Knowledge about the differences in periods of risk for congenital anomalies during a pregnancy was poor. Most participants were also not aware of the specific congenital abnormalities that are known to be caused by warfarin during pregnancy. This lack of knowledge and understanding about the serious risks associated with warfarin in pregnancy,

does not form a good platform to make informed decisions from for these high risk women. This is likely a contributing factor to the poor contraceptive practices and family planning choices that are seen in this group.

The risk of having an affected child was either overestimated by *n* = 51/101 (50.5%) or underestimated *n* = 30/101 (29.7%). One explanation could be the poor concept of risk in our study population. International studies found that both health care providers and the public did not have accurate estimates of the risks in pregnancy of different types of common medications and substances.[10,11,19]

Attitudes

A general attitude of wanting information given, but not asking for it, was found among the study participants. This was reflected in the low percentage of women having asked for contraceptive advice, as well as in the explanations as to why they did not have enough information about the effects of warfarin in pregnancy. Most participants *n* = 69/101 (68.3%) felt that the responsibility of information delivery should fall on the caring doctor. This suggests that most participants had a passive attitude, rather than active participation in the information attaining process.

The majority of women *n* = 81/101 (80.2%) wanted more information about the teratogenic effects of warfarin in pregnancy. This finding indicates that the population is receptive to counselling and information giving. This opens a window of opportunity to address these issues. Using the correct method of information delivery for the specific target group of patients is very important. Our study population had a preference for personal counselling sessions translated to their home language. This is in line with the opinions of women in an international study done in Pennsylvania in the United States.[20]

Conclusion

Language barriers, poor understanding of basic terminology and mathematics, poor contraceptive and family planning practices, lack of knowledge regarding the risks of warfarin in pregnancy and passive attitudes towards information attainment are patient related challenges that were identified in this study.

In order to decrease the incidence of these potentially avoidable congenital abnormalities and pregnancy losses due to the teratogenic effect of certain medications, one would have to address these challenges. Awareness of the teratogenic potential of specific chronic medications among all levels of health care providers, patients and the public would need to be improved. Health care providers involved in the care of women of reproductive age that might be exposed to teratogenic substances, including nursing staff and pharmacists, need to be aware of and skilled in portraying basic concepts, including risks and uncertainties. This requires special training, starting from an undergraduate level. Enough translators or health care providers fluent in local languages are necessary to overcome the language barriers we face in the health care system.

Patients and the public need improved education regarding appropriate contraceptive methods and family planning to allow them to make informed pregnancy choices and prevent

unplanned pregnancies.

Pre-conception care should be prioritised in high risk women in order to optimise care prior to conception.[21] Access, availability and appropriate referral to Genetic Counselling services and Feto-Maternal clinics would also help to ensure that these patients are managed correctly prior to and during pregnancies.

We can truly make a difference in reducing the incidence of birth defects by adjusting practices and following a person-centered care approach tailored to the needs of our local population.

Limitations

This study was conducted at a single tertiary centre with a specific population profile among a small sample of participants. The results will not necessarily be valid for other populations at different levels of care or with differing demographic profiles. Further studies are recommended among a larger population, between multiple centres and among women exposed to various other teratogenic substances.

The answers given by the women in the study group relied on their own recollection and were not confirmed by medical records. This might not be an accurate reflection of the services that they received or the outcomes of their pregnancies.

Recommendations

We recommend further research to explore the practice, knowledge and attitudes of health care professionals involved in initiating women of reproductive age on teratogenic medication. Standardised national management protocols for women of reproductive age initiated on teratogenic medications should be implemented in all levels of health care.

Acknowledgements: We would like to acknowledge R Nel from the Department of Biostatistics, UFS, who assisted with the statistical analysis in this study. ME Motloheloa and ME Gono were of great assistance with the collection of data. J Bezuidenhout from the Division of Health Sciences Education, and A Vorster, Clinical Psychologist, Support Staff School of Medicine, UFS, assisted with editing of the document.

Conflict of interest: None

Author contributions: MC was the main author. BDH and CvW assisted with conceptualisation, editing and feedback throughout the research process.

Funding sources: School of Medicine, UFS.

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Appendix A: Ethics Approval

UNIVERSITY OF THE
FREE STATE
UNIVERSITEIT VAN DIE
VRYSTAAT
YUNIVESITHI YA
FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

IRB nr 00006240
REC Reference nr 230408-011
IORG0005187
FWA00012784

08 February 2016

DR M CONRADIE
DIVISION CLINICAL GENETICS
DEPARTMENT OF NEUROLOGY
FACULTY OF HEALTH SCIENCES
UFS

Dear Dr Conradie

ECUFS NR 205/2015
DR M CONRADIE
DIVISION CLINICAL GENETICS, DEPARTMENT OF NEUROLOGY
PROJECT TITLE: TERATOGENIC MEDICATION – ARE WOMEN ADEQUATELY INFORMED ABOUT THE RISKS IN PREGNANCY?

1. You are hereby kindly informed that, the Health Sciences Research Ethics Committee (HSREC) approved the above project after all conditions were met when the signed permission letter from the Free State Department of Health was submitted. This decision will be ratified at the meeting scheduled for 23 February 2016.

2. The Committee must be informed of any serious adverse event and/or termination of the study.

3. Any amendment, extension or other modifications to the protocol must be submitted to the HSREC for approval.

4. A progress report should be submitted within one year of approval of long term studies and a final report at completion of both short term and long term studies.

5. Kindly use the ECUFS NR as reference in correspondence to the HSREC Secretariat.

6. The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

Yours faithfully

.....
DR SM LE GRANGE
CHAIR: HEALTH SCIENCES RESEARCH ETHICS COMMITTEE

health
Department of Health
FREE STATE PROVINCE

26 January 2016

Dr M Conradie
Division Clinical Genetic
Dept of Neurology
Faculty of Health Sciences
UFS

Dear. Dr Conradie

Subject: Teratogenic Medication – are women adequately informed about the risks in pregnancy?

- Permission is hereby granted for the above – mentioned research on the following conditions:
- Participation in the study must be voluntary.
- A written consent by each participants must be obtained
- Serious adverse events to be reported and/or termination of the study.
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and no names will be used.
- Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** khusemj@fshealth.gov.za or sebeelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution managers/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 1/02/2016

Appendix B1: Study Information Document

Information document

Teratogenic medication – are women adequately informed about the risks in pregnancy?

Dear Participant,

We, the department of Clinical Genetics at Universitas Hospital, are doing research on women, aged between 15 and 49 years, using warfarin treatment. Research is just the process to learn the answer to a question. In this study we want to learn what the knowledge, attitudes and practice is of women that could potentially fall pregnant, using warfarin treatment. This is not part of your usual care at the hospital and will not influence your care in any negative way. The information we are collecting is very important in order to help us to improve the care and counselling that you and other patients receive from your health care professional regarding the implications of warfarin in pregnancy. The hope is that in the long run the information will help to give women taking potentially harmful medications a better chance to have a healthy baby.

We are inviting you to participate in this research study. Or if the patient is between the ages of 15 to 18 years, we are asking if your child can participate in this research.

What is involved in the study?

We will ask you a set of questions in the form of a questionnaire while you are attending the INR clinic at Universitas Hospital to have your INR blood levels taken. This will be done in a private office after your (or your child's) blood has been taken, while you are waiting for the results. The questions will take about 30 minutes to complete. After this you will receive an information leaflet on the effects of warfarin in pregnancy and contraceptive guidelines. We are aiming to question 90 to 120 people in the study

Risks of being involved in the study:

The only risk associated with the study is a possibility that you may feel anxious about the information that was given to you and you may worry about the effects of warfarin in pregnancy. If you do feel very distressed, we will make sure that you see a professional about this.

Benefits of being in the study:
You will gain information that you may or may not have known before the study.

Participation is voluntary, and refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled; the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

There will be no reimbursement for participating in the study. We do not expect you to have any additional costs associated with participation in the study.

Confidentiality: Efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Ethics Committee for Medical Research.

If results are published, this may lead to cohort identification.

Contact details of researcher – for further information/reporting of study-related adverse events you can call Dr. M Conradie at (051) 4053401 or (051) 4053884.

Contact details of Secretariat and Chair: Ethics Committee of the Faculty of Health Sciences, University of the Free State – for reporting of complaints/problems: Telephone number (051) 4052812

Appendix B2: Participant Consent Form

CONSENT FORM

Teratogenic medication – are women adequately informed about the risks in pregnancy?

You have been asked to participate in a research study.

You have been informed about the study by …….. .
You have been informed that there will be no compensation for participation in the study.

You may contact Dr. M. Conradie at (051) 4053401 or (051) 4053884 at any time if you have questions about the research or if you have negative effects as a result of the research. You may contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, UFS at telephone number (051) 4052812 if you have questions about your rights as a research subject.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to terminate participation.

If you agree to participate, you will be given a signed copy of this document as well as the participant information sheet, which is a written summary of the research.

The research study, including the above information has been verbally described to me. I understand what my involvement in the study means and I voluntarily agree to participate.

_____	_____
Signature of Participant	Date
_____	_____
Signature of Witness *(Where applicable)*	Date
_____	_____
Signature of Translator *(Where applicable)*	Date

Appendix B3: Child Assent Form

CHILD ASSENT FORM

Teratogenic medication – are women adequately informed about the risks in pregnancy?

You are being asked to take part in a research study being done by the Division of Clinical Genetics that is part of the University of the Free State. In this study, we are talking to women using a medication called warfarin. All these women are able to become pregnant. If we are asking you to be a part of this, this means that you are a girl between the age of 15 years and 18 years and also using a medication called warfarin.

We have asked your parent or caregiver whether it is OK for you to participate, but now we want to see if it is OK with you.

If you decide to take part in this study, you will be asked questions about the treatment that you are on, what you know about the effects of this treatment on a baby if you should become pregnant, about ways of preventing a pregnancy and what you think about abnormalities in babies. As we want to know about the chance for you to fall pregnant, we are also going to ask if you are sexually active and using contraception. The questions will take about 30 minutes. We will do this in a private room without your parents present. All the information we collect will be kept secret and you don't have to share any of your answers with anybody else, including your parents.

We will not use your name so everything will remain private. By signing this you are showing that you understand what is going to be happening and have asked any questions you may have about the research. You can also ask questions later if you cannot think of them now. Signing this form does not mean that you have to finish the study - you can pull out from the study at any time without explaining why.

_____ _____

Child's signature Date and time

Appendix C: Questionnaire

Warfarin in pregnancy Questionnaire

Date completed (dd/mm/yy) _____

Section A: Demographics

1 What is your age? _____years

2 What is your residential suburb and town? _____

3 What is your highest level of education (highest grade completed)? _____

4 What is your current relationship status?

- ☐ Single
- ☐ In a casual relationship
- ☐ Living together
- ☐ Married/Traditional marriage
- ☐ Divorced/separated
- ☐ Widowed/partner died

5 What is your current employment status?

- ☐ Permanently employed
- ☐ Casually employed
- ☐ Unemployed

6 What is your main source of income?

- ☐ Own income
- ☐ Partner's income
- ☐ Family support/parents' income
- ☐ Government grants
- ☐ Other. Specify_____

7 What is your home language?

- ☐ English
- ☐ Sesotho
- ☐ Afrikaans
- ☐ isiXhosa/Zulu
- ☐ Other. Specify_____

Section B: Practice

8 For which medical condition are you taking Warfarin?

- ☐ Heart-valve replacement/heart surgery
- ☐ Blood clots in leg/ Deep venous thrombosis
- ☐ Pulmonary embolis/ blood clots in lungs
- ☐ Heart beating irregularly / arrhythmias
- ☐ Unsure
- ☐ Other (specify)_____

9 How long have you been taking Warfarin? _____years

10 At which hospital and department were you started on Warfarin? _____

11 Did you have a pregnancy test before starting on Warfarin? | yes | no | unsure |

12 How do you take your Warfarin?

	I always remember to take my tablets
	I sometimes forget to take my tablets
	I forget my tablets most of the time
	Someone needs to remind me, otherwise I do not take them

13 Do you take any other chronic medication?

yes	no

14 If yes, name the medication/s and when it was started: _____

_____

15 Are you sexually active? | yes | no |

16 How many times have you been pregnant? _____

G		P		M	

17 How many of your pregnancies were planned? _____

18 How many children do you have? Please specify their age

19 If any miscarriages or stillbirths, please specify. _____
State cause if known _____

20 Do you have any children with problems? | yes | no | Please specify _____

21 Have you used Warfarin previously while pregnant? | yes | no | unsure |

22 Explain how each of your pregnancies were managed.

Pregnancy nr	**1**	**2**	**3**	**4**	**5**
Year of pregnancy/age					
Gestation booked at local clinic					
Gestation referred to tertiary level					
Gestation warfarin changed					
Gestation of delivery					
Place of delivery					
Method of delivery					
Outcome of pregnancy*					

*LB = live birth; SB = stillbirth; ENND = early neonatal death;
LNND = late neonatal death; MC = miscarriage; BD = birth defects

23 Are you pregnant now? | yes | no | unsure | If unsure, when is LNM? _____

24 Are you planning any further pregnancies? | yes | no | unsure |
If yes, how many _____

25 What type of contraception are you using? (if using double contraception, indicate both)

	None
	Abstinence
	Male condoms
	Female Condoms
	Oral contraceptives
	Depo injections
	Implantable contraceptive
	Intra-uterine device
	Female surgical sterilization
	Male surgical sterilization
	Other. Please specify……..

26 If using contraception, indicate the number of methods?

	Only one type of contraception
	Using 2 different types of contraception

27 How regularly do you use contraception?

	Almost never
	Less than half of the time
	More than half of the time
	Most of the time
	Always

28 Have you ever asked for contraceptive advice?

yes	no

29 If yes, from whom did you ask advice?

	Nursing sister at local clinic
	Doctor at clinic
	Mother/grandmother
	Friend
	Other_____

Section C: Knowledge

30 Were you given information regarding the effects of warfarin in pregnancy?

yes	no

31 If yes, who gave you this information?

- [ ] Nurse/Clinic sister
- [ ] Pharmacist
- [ ] Doctor
- [ ] Genetic counsellor
- [ ] Family/friends
- [ ] School
- [ ] Newspaper/Radio
- [ ] Other. Please specify _____

32 What does "birth defects" mean to you? _____

_____

33 Do you know of anything that can cause birth defects(abnormalities in the baby) in a pregnancy? (eg. Substances taken by a mother?)

_____

34 If we talk about risk or the chance something happens, which of the following is the biggest?

- [ ] 10% chance
- [ ] One out of 10
- [ ] Ten out of a hundred
- [ ] All the same

35 Choose the best answer: If I am using Warfarin I should…

- [ ] A. Take no contraception, because the contraception will influence my treatment
- [ ] B. Not have intercourse 2 weeks after my period started
- [ ] C. Use good contraception like the depo injection
- [ ] D. I don't have to use contraception, because I cannot get pregnant when drinking Warfarin

36 What problems can Warfarin cause when taken in pregnancy?

- [ ] A. Nausea and vomiting
- [ ] B. Birth defects or abnormalities in the baby
- [ ] C. Headaches
- [ ] D. No problems

37 When I am using Warfarin and want to fall pregnant, I should…

- [ ] A. Plan the pregnancy and talk to the sister or doctor
- [ ] B. Stop my contraception
- [ ] C. Use no contraception
- [ ] D. Stop my Warfarin tablets

38 During what time in pregnancy is the chance the biggest for birth defects?

- [ ] A. First 3 months
- [ ] B. Second 3 months
- [ ] C. Last 3 months
- [ ] D. Same throughout the pregnancy

39 Can Warfarin cause abnormalities of my baby's brain if taken in pregnancy?

	Yes
	No
	Unsure

40 Can Warfarin cause the bony structure or skeleton of the baby to be abnormal?

	Yes
	No
	Unsure

41 Can Warfarin result in abnormalities of the baby's nose with breathing problems?

	Yes
	No
	Unsure

42 What other problems can Warfarin cause in pregnancy?

	A. Miscarriage
	B. Stillbirth
	C. Infant death
	D. All of the above

43 What is the chance of Warfarin causing abnormalities in the baby?

	A. 5%
	B. 30%
	C. 90%
	D. 100%

44 What type of contraception is the best to prevent a pregnancy out of the following?

	A. Male Condoms
	B. Female Condoms
	C. Depo injection every 3 months or oral contraceptives
	D. Checking the calender

Section D: Attitudes

45 Do you think you have enough information about the effects of Warfarin in pregnancy?

yes	no	unsure

46 If no, why do you think this is?

	I was never given information
	I was given information, but forgot because no written material was provided
	I did not understand the language the information was given in.
	I understood the language, but did not understand the explanation
	I did not ask for information
	Other (specify) _____

47 Who do you think should inform you about the effects of medication in pregnancy?

	Nurse
	Doctor
	Pharmacist
	All of above
	Other. _____

48 In your opinion, what would be the best way to communicate this information to patients?

	Posters up in the clinics
	Information leaflets in English
	Information leaflets in my home language
	A counselling session by my health care provider in English
	A counselling session by my health care provider translated to my home language
	Pharmacist telling me before handing out the medicine
	Warnings printed on the medication box
	Other (specify)_____

49 Would you like to have more information about the risks of your medication in pregnancy?

yes	no	unsure

50 How would you feel if you are not informed about aspects concerning your or your child's health?

_____

51 Should a woman be informed about her pregnancy choices?

	Strongly agree
	Agree
	No opinion
	Disagree
	Strongly disagree

52 In your opinion, should a woman be offered a choice to end a pregnancy if there is a birth defect?

	Strongly agree
	Agree
	No opinion
	Disagree
	Strongly disagree

53 What is your opinion on termination of pregnancy?

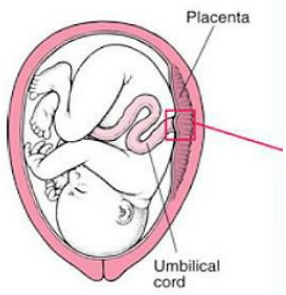
_____

Appendix D: Information Pamphlet

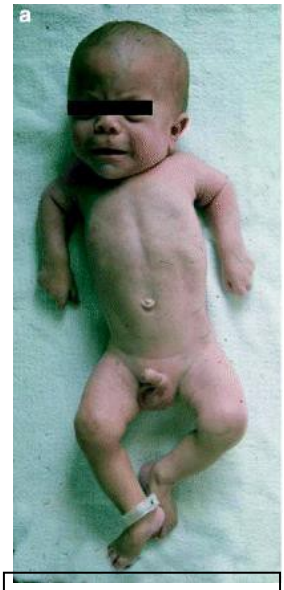
Warfarin and Pregnancy

If you are a woman below the age of 50 and taking warfarin there are a few important things you should know about this medication:

Warfarin is a medication that lowers the blood's ability to form a clot. If you have been prescribed warfarin this means that you have either an increased risk of blood clotting or you have had a heart valve replacement or you have have blood clots through your lungs. This medication is potentially life-saving for you and can prevent a stroke, heart attack or unwanted blood clots in your veins.

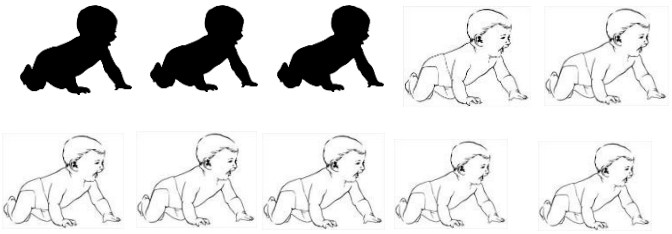


If you are pregnant, warfarin can cross the placenta and potentially affect your unborn baby. With exposure early in pregnancy, one can have an increased chance of a miscarriage. It can also cause birth defects by affecting the development of the baby's skeleton and the baby might have a deep nose bridge or shortened limbs. At any time in the pregnancy the medication can lower the ability of the baby's blood to clot and cause bleeding inside the brain. This can have serious effects on the child's long term mental abilities or structure of the brain. There is also a risk for a miscarriage, stillbirth and a few other less common problems.



Short upper arms and legs [http://static-content.springer.com/image]

The chance of a healthy baby when using warfarin throughout the pregnancy is 70% or 7 out of 10.



Between the time that a girl reaches maturity and that your periods stop completely at the age of 45 to 55 years, you could fall pregnant if you have unprotected sexual intercourse. If you can potentially get pregnant it is very important to use good contraception to prevent an unplanned pregnancy. The safest is use 2 types of contraception at the same time. For instance any of the contraceptive measures below plus a male condom, as this will also protect against sexually transmitted diseases.

The best contraceptive measures, with the lowest chance of falling pregnant, available in the government sector are:

- Intrauterine copper T-device (inserted in the uterus and is effective for 5 to 10 years depending on the type used)
- Implantable contraceptive (implant in the arm that lasts 3 years)
- 2 – 3 monthly Depo injections
- Surgical sterilization only if your family is completed
- Combined oral contraceptives used EVERY day at the SAME time (but this is difficult and therefore not as reliable)

If you do WANT to fall pregnant the following are very important:

- NEVER stop your warfarin without discussing this with your doctor. This could have serious consequences to your health if you do.
- ALWAYS plan the pregnancy.
- There are other options that include using Heparin injections daily for the whole or part of the pregnancy, BUT this depends on your medical condition. The best plan for YOU AND YOUR BABY will be worked out by your doctor when a pregnancy is desired.
- You will need HIGH RISK follow up in the pregnancy at a tertiary level hospital.
- If you ARE pregnant, you need to be referred to the High Risk antenatal clinic URGENTLY.

Further information:

For further discussion about the risks and options regarding warfarin and pregnancy, you can make an appointment at the Genetics clinic at Universitas hospital on 051-4053401 (Mondays, Thursdays) or 051-4053204 at the Antenatal clinic.

Information leaflet compiled by Dr. M Conradie, Division Clinical Genetics, Universitas Hospital, Free State, in November 2015.

Advice for future pregnancies: (for all women)

- I must get my Rubella vaccine (immunization) NOW or have my Rubella antibodies tested (at Local clinic/GP). If my antibodies are high enough, I do not need a vaccine. If low, I do need a Rubella vaccine. Do not fall pregnant within 3 months of vaccine.
- Plan the pregnancy.
- Before I get pregnant I should check my HIV status, blood pressure, glucose and check that if I am on chronic medication that it is safe in pregnancy (at Local clinic/GP).
- I need to get Folic Acid from the clinic/pharmacy and start drinking it 3 months before I try to get pregnant (take 1 tablet daily). Continue the Folic Acid through the pregnancy.
- Before taking any medicines during pregnancy, ask your GP/Clinic/Pharmacist if it is safe.
- Try to avoid children with fever and rashes when pregnant.
- I must NOT drink ANY alcohol just before or during the pregnancy. Alcohol will harm my unborn baby's brain and other organs.
- I must NOT smoke or use any recreational drugs while pregnant.

Appendix E: SAMJ Author Guidelines

SAMJ Author Guidelines

http://www.samj.org.za/index.php/samj/about/submissions

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

Structured abstract

This should be 250-400 words, with the following recommended headings:

Background: why the study is being done and how it relates to other published work.
Objectives: what the study intends to find out
Methods: must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
Results: first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
Conclusion: must be supported by the data, include recommendations for further study/actions.

Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.

Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

Start with description of the population and sample. Include key characteristics of comparison groups.

Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.

Do not replicate data in tables and in text.

If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows: E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).

Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
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    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references:
    - Government Gazettes:

      National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No.17507:1514. 1996.

      In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

    - Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

* Acts:

South Africa. National Health Act No. 61 of 2003.

* Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

* Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

* Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

* Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'